REMARKS

Applicants have amended the specification merely to correct a typographic error.

Applicants have amended claims 75, 91, 94, 99, and 123-124 mainly for greater clarity. The claim amendments are fully supported by the original specification (e.g., page 4, lines 11-15; and page 8, lines 18-21) and original claims (e.g., claim 76). No new matter has been introduced and no new issue has been raised. The amendments are made solely to expedite prosecution of the application and Applicants reserve the right to pursue subject matter as originally claimed in the present or future applications.

Applicants note that the previous amendments filed on February 16, 2007, May 22, 2007, and August 21, 2007 were entered.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Election/Restriction

The Examiner has acknowledged the decision on petition to withdraw the requirement to restrict and elect a single species as set forth in the Office Action mailed May 3, 2006.

Priority

The Examiner asserts that claims 75, 84-91, 93-102, 104-106, and 123-124 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents cited, since these claims stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description and a sufficiently enabling disclosure. The Examiner has deemed the effective filing date of the above-mentioned claims as the filing date of the instant application: August 26, 2003. See Office Action, page 4, second paragraph.

First of all, Applicants point out that in the Office Action mailed December 19, 2006, the Examiner asserted that only claims 86, 87, 98, and 99 do not properly benefit under 35 U.S.C. § 120

by the earlier filing dates of the priority documents cited, and deemed the effective filing date of claims 86, 87, 98, and 99 as the filing date of the instant application: August 26, 2003. Clarification is respectfully requested. Applicants traverse the Examiner's priority rejection only with respect to claims 86, 87, 98, and 99.

Applicants reiterate the arguments already made of record and submit that the parent applications (Serial Nos. 10/274,177 and 10/229,345) as filed are fully compliant with the requirements of the first paragraph of 35 U.S.C. § 112. Thus, the effective filing date of the pending claims should be the filing date of the earliest priority application: August 26, 2002. Applicants reserve the right to traverse the Examiner's assertion upon indication of allowable subject matter or upon application of an intervening reference; at which point, Applicants will provide supportive priority documents if deemed necessary.

Applicants note that the Examiner has agreed that claim 87 would properly benefit from the filing date of Application No. 10/229,345 (August 26, 2002), if the rejections under 35 U.S.C. § 112, first paragraph, were obviated.

Claim Objection

In an effort to expedite prosecution, Applicants have amended claim 99 as suggested by the Examiner, rendering the objection moot.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 75 is alleged to be indefinite because the recitation "the nucleic acid" lacks proper antecedent basis. Applicants have amended claim 75 by removing such recitation, rendering the objection moot. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 75, 84-91, 93-102, 104-106, and 123-14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Examiner asserts that "[c]laims 75, 84-91, 93-102, 104-106, 123, and 124 are directed to a genus of secreted polypeptides that are produced by the expression of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5." See Office Action, page 8, last two paragraphs. In particular, the Examiner asserts that "if not a polypeptide comprising the amino acid sequences of SEQ ID NO: 3 and/or SEQ ID NO: 21, the specification fails to describe with any of the requisite degree of clarity and particularity the structures of the secreted 'ColoUp2' polypeptides that encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5." See Office Action, page 10, third paragraph.

Applicants respectfully disagree. Nevertheless, solely to expedite prosecution, Applicants have amended independent claim 75, step (b), to specify that said at least one secreted ColoUp2 polypeptide is selected from the group consisting of: (i) a secreted polypeptide having an amino acid sequence at least 95% identical to SEQ ID NO: 21, and (ii) a secreted polypeptide having an amino acid sequence ~~of~~ at least 95% identical to SEQ ID NO: 3. The claim amendments are fully supported by the original specification (e.g., page 4, lines 11-15; and page 8, lines 18-21) and original claims (e.g., claim 76). Applicants believe the claim amendments obviate this ground of the rejection.

The Examiner appears to be asserting that because not all ColoUp2 secreted polypeptide sequences are disclosed, the written description is deemed to be incomplete. However, what is required by the most recent version of the *Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement*, which appeared in the Federal Register in January 2001, Vol. 66, No. 4, pp. 1104-1111, is only:

> "sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., **or** by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus...." (emphasis added)

While the Examiner appears to be requiring physical and/or chemical properties, these are obviously not required by the Guidelines – the relevant structures have been disclosed, not to mention actual reduction to practice of several species within the claimed genus. Applicants point

out that the secreted ColoUp2 polypeptide as recited in amended claim 75 is structurally defined. Moreover, the specification provides sufficient description of the ColoUp2 polypeptides for the purposes of the claimed method, including full-length and processed forms of the ColoUp2 polypeptide as well as fragments thereof (e.g., page 19, lines 14-24; page 34, lines 3-18; and page 40, lines 5-16). The specification also provides working examples for the method as recited in amended claim 75 (see, e.g., Example 7 on pages 53-54 and Examples 10-13 on pages 54-57).

Applicants draw the Examiner's attention to a recent PTO Board decision, which supports Applicants' position that the specification provides adequate written description for the recited genus of secreted ColoUp2 polypeptides in the amended claims. *See Ex parte Bandman*, No. 2004-2319, (BPAI 2005). Claims 3 of the U.S. Application No. 09/915,694 ('694 application) in *Bandman*, which was representative of the subject matter on appeal, recites, *inter alia*, "an isolated polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1." In *Bandman*, Applicants appealed a Final rejection by the Examiner, and the Board reversed the rejections based on both the written description and enablement requirements of 35 U.S.C. § 112, first paragraph to one of the claims on appeal. Pointedly, the Board found that claims directed to a naturally occurring amino acid (or polynucleotide) sequence at least 95% identical to the disclosed amino acid (or polynucleotide) sequence were enabled and met the written description requirement, even in the absence of explicitly reciting a *functional requirement* of the claimed sequences. The Board noted that "[t]he written description requirement . . . does not require a description of the complete structure of every species within a chemical genus." *Bandman*, No. 2004-2319 at p. 3. The Board also compared the circumstances of *Bandman* with those faced by the Federal Circuit in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002). In *Enzo Biochem*, the Federal Circuit determined that an "[a]dequate written description may be present for a genus of nucleic acids based on their hybridization properties, 'if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar.'" (citing *Enzo Biochem*, 296 F.3d at 1324). Thus, in *Bandman*, the Board

determined that the genus of molecules defined by the claims was similarly limited, and reversed the Examiner's written description rejection.

The Examiner further asserts that "the specification only shows that transfected cell lines, which have been engineered to express a nucleic acid molecule encoding the full-length polypeptide of SEQ ID NO: 14, secrete the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 . . . it fails to demonstrate the presence of either polypeptide in the blood, or a fraction thereof, urine, or stool of a subject known to have any precancerous or cancerous growth of the colon." See Office Action, page 17, lines 13-19.

Applicants respectfully disagree. Contrary to the Examiner's assertion, the specification amply teaches that ColoUp2 is a secreted protein and useful as a colon neoplasm diagnostic marker, for example, for blood, plasma, serum, or stool tests (e.g., page 5, lines 9-14; page 9, lines 10-20; page 32, lines 19-22; the paragraph bridging pages 32 and 33; and page 45, lines 23 - page 47, line 31). Not only does the specification provide working examples to show that ColoUp2 was secreted, the specification also provides working examples to show that at least two secreted forms of ColoUp2 protein were successfully detected in the culture medium of cells and in the blood from a mouse bearing tumor xenografts. In view of the teachings of the specification, one of skill in the art would know that Applicants were in possession of the claimed invention at the time this application was filed.

In sum, Applicants believe the claim amendments have obviated the written description rejection. Applicants respectfully request reconsideration and withdrawal of all rejections for lack of written description.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 75, 84-91, 93-102, 104-106, and 123-14 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Examiner asserts that "the claims are directed to a genus of secreted 'ColoUp2' polypeptides, which are encoded by a nucleic acid molecule comprising the nucleotide sequence of

SEQ ID NO: 5, but which differ both structurally and functionally." See Office Action, page 20, third paragraph.

As described above, Applicants have amended independent claim 75 to specify that said at least one secreted ColoUp2 polypeptide is selected from the group consisting of: (i) a secreted polypeptide having an amino acid sequence at least 95% identical to SEQ ID NO: 21, and (ii) a secreted polypeptide having an amino acid sequence ~~of~~ at least 95% identical to SEQ ID NO: 3. Applicants believe the claim amendments have obviated the enablement rejection.

Further, the Examiner asserts that the specification fails to demonstrate the presence of any one of the "ColoUp2" polypeptides (e.g., the polypeptide of SEQ ID NO: 3) in any biological sample, such as blood, urine, or stool acquired from subjects known to have a colonic polyp, a colon adenoma or a colon carcinoma. See Office Action, page 21, lines 4-7.

Applicants respectfully disagree. The specification as filed is enabling for the full scope of the claimed invention. As described above, the specification teaches that secreted ColoUp2 polypeptides could be successfully detected in the culture medium of transfected cells and in the blood of mice implanted with transfected xenograft tumor cells. Moreover, the specification teaches how to detect secreted ColoUp2 polypeptides in biological sample, and in particular, how to use an antibody in an immunoassay for detecting secreted ColoUp2 polypeptides (e.g., page 5, lines 9-14; page 9, lines 10-20; page 32, lines 19-22; the paragraph bridging pages 32 and 33; and page 45, lines 23 - page 47, line 31). Further, the level of skill in the art was high at the time of the filing date of the present application. In fact, the techniques involved in the invention, all of which were well known in the art even before the filing date, are highly reliable and can be readily practiced by a skilled artisan.

In addition, Applicants enclose herewith as **Exhibit A** results which demonstrate successful detection of ColoUp2 polypeptides in biological samples (e.g., serum) acquired from colon cancer patients. In addition, these results show that following surgical removal of the colon cancer, the circulating ColoUp2 level fell in all patients. These results also show that in the majority of cases, ColoUp2 is a better marker of colon cancer than CEA (a known cancer marker) since ColoUp2 showed a greater decline in the circulating level after removal of the colon tumor than CEA. The

graph on Exhibit A shows 31 colon cancer cases. In each case, CEA and ColoUp2 levels were measured before the surgery for colon cancer removal (pre-op) and then on day 5 after the surgery (post-op). The graph shows pre-op marker value/post-op marker value. CEA is on the Y axis and ColoUp2 on the X axis. The line identifies where the fall in CEA was the same as the fall in ColoUp2. Samples above the line are ones where CEA fell more than ColoUp2. Samples below the line are samples where ColoUp2 fell more than CEA. Only in 9 cases (i.e., those above the line), CEA was the better marker than ColoUp2. However, in 18 out of 31 cases (i.e., those below the line), ColoUp2 fell more than CEA and was a better marker for colon cancer than CEA.

In addition, Applicants remind the Examiner that there is no legal requirement to test the efficacy of all biological samples of the claimed invention to show the operativeness. The law does not impose such a formidable burden on inventors seeking patent protection. "Appellants (here, Applicants) are not required to disclose every species encompassed by their claims even in an unpredictable art" (emphasis original). *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976). Such a holding is only reasonable, since it is very difficult, if not impossible, to test and disclose all operative species in the chemical and biotechnology fields. As further pointed out by the Angstadt court "[w]ithout undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them." Id, at 219.

In sum, Applicants contend that the pending claims are enabled throughout their scope. Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

Claims Rejections under 35 U.S.C. § 102(e)

Claims 75, 84-87, 89-91, 93-98, 100-102, 104-106, and 123-124 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by US 2004/0005563 (Mack et al., referred to herein as the '563 application). Applicants respectfully traverse the rejection.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth

in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1978).

Applicants contend that the '563 application fails to satisfy the criteria for anticipating the present invention. The '563 application describes hundreds of gene markers (including ColoUp2) and related methods for diagnosis and treatment of ovarian cancer (see, e.g., the title and the abstract). However, the '563 application does **not** teach or suggest a method for determining whether a subject is likely to have a colon neoplasm based on the presence of a secreted ColoUp2 polypeptide. In fact, the '563 application is entirely silent on **colon neoplasm** as recited in claim 75. Applicants point out that the term "colon neoplasm" constitutes structural limitations of claim 75 since it is recited in both the preamble and the wherein clause of claim 75. Accordingly, the '563 application does not teach all the elements of independent claim 75. For the same reasons, all claims depending from claim 75 are not anticipated by the '563 application. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims Rejections under 35 U.S.C. § 102(a)

Claims 75, 84-87, 89-91, 93-98, 100-102, 104-106, and 123-124 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by WO 2002/068677 (Mack et al., referred to herein as the '677 application). Applicants respectfully traverse the rejection.

Specifically, the Examiner asserts that "WO 2002/068677 A1 (Mack et al.) teaches a secreted polypeptide comprising an amino acid sequence of SEQ ID NO: 3 and which comprises the amino acid sequence of SEQ ID NO: 21 . . . Mack et al. teaches detecting colon cancer in a subject by acquiring a biological sample (e.g., a sample of blood, serum, or stool) and determining if the secreted polypeptide is present in the sample using an immunoassay that employs a labeled or unlabeled antibody that binds to the polypeptide." Office Action, page 28, last paragraph.

First of all, Applicants submit that the Examiner has incorrectly characterized the '677 application as 102(a) prior art. As argued above under the "Priority" section, the effective filing date of the pending claims should be the filing date of the earliest priority application: August 26,

2002 because the pending claims properly benefit by the earlier filing dates of the priority documents cited. By contrast, the '677 application was published on September 6, 2002, after the effective filing date of this application. Thus, the '677 application is disqualified as 102(a) prior art.

In fact, the Examiner has withdrawn the § 102(a) rejection in the Office Action mailed December 19, 2006, acknowledging that "because the effective filing date of the claims is presently regarded as the filing date of the earlier filed U.S. Patent Application No. 10/229,345, namely August 26, 2003, and accordingly **Mack et al. [WO 2002/268677]** which was published September 6, 2002, is **not prior art under § 102(a)**" (see, page 4, lines 11-16, emphasis added).

Assuming for argument's sake that the '677 application qualified as 102(a) prior art, the '677 application does not teach all the elements of the claims. The '677 application lists genes that are either upregulated or downregulated in metastatic colon cancer (liver metastasis) compared to normal or non-metastatic colon samples (see, e.g., Tables 1-26). However, the '677 application does **not** teach which genes (e.g., up- or down-regulated genes) to detect in order to determine whether a subject is likely to have colon neoplasia. Page 25 of the '677 application states "[i]n a preferred embodiment, metastatic colorectal cancer sequences are those that are *up-regulated* in metastatic colorectal cancer..." and page 26 states "In another preferred embodiment, metastatic colorectal cancer sequences are those that are *down-regulated* in the metastatic colorectal cancer..." (*emphasis added*). Further, on pages 7-8, the disclosure recites "Alteration of gene expression for a gene from Tables 1-26 may be *more likely or less likely* to indicate that the subject will progress to metastatic disease....Alteration of gene expression for a gene from Tables 1-26 *may or may not* indicate that the subject is more likely to progress to cancer or to metastatic disease" (*emphasis added*). Thus, the '677 application fails to teach any correlation between a specific sequence of Tables 1-26 (including ColoUp2 as set forth in SEQ ID NO: 23) and a subject's likelihood of having colon neoplasia, and fails to anticipate the claimed invention.

Moreover, contrary to the Examiner's assertion, the '677 application does not disclose SEQ ID NO: 3. The Examiner appears to assert that SEQ ID NO: 23 of the '677 application is identical to SEQ ID NO: 3 of the instant application. However, SEQ ID NO: 23 of the '677 application

differs from SEQ ID NO: 3 of the instant application at the C-terminal end, where amino acids FLRRP of SEQ ID NO: 3 are replaced with a 30 amino acid sequence (amino acids 751-780 of SEQ ID NO: 23).

In sum, the '677 application is both disqualified as 102(a) prior art and fails to teach all the elements of independent claim 75. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims Rejections under 35 U.S.C. § 102(a)

Claims 75, 84-87, 89-91, 93-102, 104-106, and 123-124 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by WO 2002/86443 (Aziz et al., referred to herein as the '443 application). Applicants respectfully traverse the rejection.

First of all, Applicants submit that the Examiner has incorrectly characterized the '443 application as 102(a) prior art. As described above, the effective filing date of the pending claims should be the filing date of the earliest priority application: August 26, 2002. By contrast, the '443 application was published on October 31, 2002, after the effective filing date of this application. Thus, the '443 application is disqualified as 102(a) prior art.

Assuming for argument's sake that the '443 application qualified as 102(a) prior art, the '443 application does not teach all the elements of the claims. The '443 application describes hundreds of gene markers (including ColoUp2) and related methods for diagnosis and treatment of lung cancer (see, e.g., the title and the abstract). However, the '443 application does **not** teach or suggest a method for determining whether a subject is likely to have a colon neoplasm based on the presence of a secreted ColoUp2 polypeptide. In fact, the '443 application is entirely silent on **colon neoplasm** as recited in claim 75. The term "colon neoplasm" constitutes structural limitations of claim 75 since it is recited in both the preamble and the wherein clause of claim 75. Accordingly, the '443 application does not teach all the elements of independent claim 75.

Moreover, contrary to the Examiner's assertion, the '443 application does not disclose SEQ ID NO: 3. The Examiner appears to assert that SEQ ID NO: 87 of the '443 application is identical

to SEQ ID NO: 3 of the instant application (Office Action, page 29, lines 17-18). However, SEQ ID NO: 87 of the '443 application has only 507 amino acids, which clearly differs from SEQ ID NO: 3 of the instant application.

In sum, the '443 application is both disqualified as 102(a) prior art and fails to teach all the elements of independent claim 75. Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the amendments and at least the forgoing remarks, Applicant believes the pending claims are in condition for allowance. If any additional fees are due, please charge our Deposit Account No. 18-1945, under Order No. **CWRU-P03-003** from which the undersigned is authorized to draw.

Dated: January 29, 2008

Respectfully submitted,

By _____

Z. Angela Guo
Registration No.: 54,144
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorney For Applicant